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Linking lncRNA to genomic stability

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Long Non-coding RNAs (lncRNAs), usually derived from intergenic regions or introns, play distinct and important roles in diverse biological processes. Up to now, many types of non-coding RNAs have been identified across species. They are highly heterogeneous in their lengths, structures, and functions. Aberrant regulation of lncRNAs has been shown to be associated with human diseases, such as cancer, but the mechanisms have remained largely unknown (Rinn and Chang 2012). A recent study from Mendell and colleagues published in *Cell* dissected a novel pathway in which a specific lncRNA, termed NORAD, protects cells from becoming aneuploid (Lee et al., 2016), which is known to drive the occurrence and development of cancer, among other diseases. Their findings not only establish a new mechanism by which lncRNAs control chromosome segregation, but also advance our understanding of the underlying causes of aneuploidy.

High-fidelity chromosome segregation requires the proper execution and coordination of several chromosomal processes, including proper kinetochore-microtubule attachment and sister chromatid cohesion that maintains the physical linkage between sister chromosomes until their separation. The centromere is comprised of repetitive DNA sequences. It is bound by the centromere-associated network (CCAN) of centromere proteins, including CENP-A and CENP-J. CCAN initiates the assembly of the kinetochore that provides the major microtubule binding sites on chromosomes. Proper kinetochore-microtubule attachment is essential for accurate chromosome segregation. Wrong kinetochore-microtubule attachments can lead to chromosome missegregation and aneuploidy.

Sister chromatid cohesion is mediated by the conserved cohesin complex consisting of SMC1, SMC3, SCC1, and SA1/2 in humans. Cohesin is loaded onto chromosomes in telophase or early G1 phase of the cell cycle. Establishment of sister chromatid cohesion occurs during S phase, and this process requires acetylation of the SMC3 cohesin subunit by ESCO1/2 and the positive cohesion regulator, Sororin. Binding of Sororin to cohesin antagonizes the function of the negative cohesion regulator, WAPL, thus establishing sister chromatid cohesion. During mitosis, cohesion must be properly resolved to allow sister chromatids to separate. In prophase, most of the cohesin on chromosome arms is phosphorylated by multiple mitotic kinases. Phosphorylation of cohesin leads to its release from chromosome arms in a WAPL-dependent manner (Zheng and Yu, 2015). At centromeres, cohesin is protected by the cohesin protector, SGO1, until anaphase onset when centromeric cohesin is cleaved by Separase (Zheng and Yu, 2015).

Because of their essential functions in chromosome segregation, the centromere proteins and the cohesin network are critical for genomic stability and must be tightly regulated during cell division. The work by Mendell and colleagues now establishes that the expression of these genes is regulated by a novel lncRNA, named NORAD (Lee et al., 2016). They found that knocking out NORAD significantly decreased the expression of a set of genes necessary for maintaining genomic stability. Consequently, a higher rate of aneuploidy was observed in NORAD knockout cells.

NORAD was originally identified in the mouse and was shown to be induced by DNA damage in a p53-dependent manner, suggesting that it might play a role in DNA damage response. Similarly, NORAD in human cells was also in-

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duced by DNA damage in a p53-dependent manner. On the other hand, absolute copy-number analysis in human cells without DNA damage showed that NORAD was present at a high number comparable to that of the housekeeping gene *ACTB*, consistent with an important function of NORAD during the unperturbed cell cycle.

To understand how NORAD regulates the expression of genes necessary for maintaining genomic stability, Mendell and colleagues analyzed NORAD-associated proteins with mass spectrometry and identified the PUMILIO proteins, PUM1/PUM2. PUM1/2 are known RNA-binding proteins. They bind to the 3′-UTRs of target mRNAs through their PUMILIO homology domains, thereby inhibiting translation. To confirm if NORAD regulates the expression of genome-stability genes through PUM1/2, Mendell and colleagues performed genetic analysis of NORAD and PUM1/2. They found that knocking out NORAD hyper-activated PUM2, as evidenced by the downregulation of PUM2 targets, including ESCO2, SMC1/3 and CENP-J. Moreover, overexpression of PUM1 or PUM2 significantly decreased the expression of PUM2 targets, mimicking the phenotypes of NORAD knockout cells. Taken together, these results establish a novel lncRNA-regulated pathway that maintains genomic stability. In this pathway, the lncRNA NORAD physically binds to PUM1/2 to suppress their binding activities towards mRNAs of many genes, including those necessary for maintaining genomic stability (Lee et al., 2016). As a result, the expression of these important genes and the genomic stability of cells are maintained. Thus, the delicate balance between the opposing functions of NORAD and PUM1/2 is for critical for the maintenance of genomic stability.

The work from Mendell and colleagues raises many interesting questions to be addressed in the future. First, although it has been shown that NORAD is important for maintaining genomic stability at the cellular level, whether this is the case at the organismal level is unknown. Genetic ablation of NORAD in the mouse will be very informative in this regard. Second, it will be interesting to test whether if NORAD has a role in regulating DNA damage response, as it is induced by DNA damage. Third, the aneuploidy phenotype of NORAD knockout cells may be caused by the combined effect of down-regulating many genes, as knocking out NORAD significantly affects the expression of a large set of genes (Lee et al., 2016). It will be both challenging and rewarding to identify the relevant targets of the NORAD-PUM1/2 pathway in genome maintenance.

The centromere is traditionally thought to be heterochromatic and transcriptionally silent, but increasing evidence suggests that there is active transcription at centromeres, which produces α-satellite RNAs. Lengths of these noncoding α-satellite RNAs are usually more than several hundred nucleotides and can be considered as lncRNAs. A recent study identified a specific α-satellite RNA with a length of 1.3 kb that physically binds to the HJURP/CENP-A complex, thus facilitating the incorporation of CENP-A into centromeric chromatin (Quenet and Dalal, 2014). In addition, α-satellite RNAs *in vitro* can also interact with the cohesin protector, SGO1, an essential effector for maintaining chromosome stability (Liu et al., 2015). Because of the well-established functions of CENP-A and SGO1 in proper chromosome segregation, α-satellite RNAs represent another type of lncRNAs that are important for maintaining genomic stability. In the future, it will be important to systematically explore whether additional lncRNAs are involved in maintaining genomic stability. This may provide us with a comprehensive view of how de-regulation of lncRNAs contributes to aneuploidy and tumorigenesis.

Aberrant regulation of lncRNAs usually occurs in cancer cells, but the consequences and molecular mechanisms of this dysregulation remain obscure. The seminal discovery of the NORAD-PUMILIO genome-maintenance pathway by Mendell and colleagues enables future studies on the underlying causes of cancer caused by aberrant regulation of lncRNAs, and paves the road for additional exciting discoveries for years to come.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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